Immune reconstitution syndrome and fungal infections

Ashish O. Gupta[a] and Nina Singh[b]

[a]Division of Hematology and Oncology, Children's Hospital of University of Pittsburgh and [b]VA Pittsburgh Healthcare System, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Correspondence to Nina Singh, MD, Infectious Diseases Section, VA Medical Center, University Drive C, Pittsburgh, PA 15240, USA
Tel: +1 412 360 1688; fax: +1 412 360 6950;
e-mail: nis5@pitt.edu

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Purpose of review

Fungal infections-related immune reconstitution syndrome (IRS) poses challenging diagnostic and management issues in immunocompromised hosts. This review summarizes the current state of knowledge regarding its pathophysiologic basis, presentation, and treatment strategies.

Recent findings

Existing evidence suggests that IRS is a state of an imbalance between protective immunity and inflammatory pathology versus anti-inflammatory responses that restrain inflammation. IRS has been observed in diverse hosts including HIV-infected patients initiating potent antiretroviral therapy, transplant recipients, pregnant women, and recipients of iatrogenic biologic agents. Among the most common fungal infections associated with IRS is cryptococcosis, although this entity has been documented during the course of invasive aspergillosis, histoplasmosis, and candidiasis. Unique risk factors for IRS have been recognized in specific hosts.

Summary

IRS is a culmination of immunologic sequelae of host–pathogen interaction during evolution of an opportunistic infection, and as such the development of biomarkers that differentiate it from progressive disease would represent an important advance. Optimal management of immunosuppression and immunomodulatory approaches that target precise regulatory pathways for IRS warrant future investigations.

Keywords

fungal infections, HIV, immune reconstitution syndrome, mycoses, transplants

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Introduction

Inflammation is an essential component of the protective immunity to microbes. However, restoration of host immunity during treatment of microbial infections may promote excessive inflammatory pathology and potentially tissue damage. The ensuing clinical entity termed immune reconstitution syndrome (IRS) has emerged as a significant complication in diverse hosts. IRS has been reported in HIV-infected patients initiating antiretroviral therapy (ART), transplant recipients, neutropenic patients, pregnant women, and recipients of immunomodulatory biologic agents [1•,2,3]. The review herein summarizes the current state of knowledge regarding the pathophysiologic basis, clinical characteristics, risk factors, potential biomarkers, and management strategies of IRS associated with fungal infections.

Pathogenesis

T-helper (Th) effector and regulatory cells are regarded as key contributors to the pathogenesis of IRS. Traditionally, Th1 that elicit proinflammatory responses and Th2 that promote an anti-inflammatory milieu have been recognized as the key functional subsets. Two additional lineages of Th cells, that is, Th17 and regulatory T (Tregs) cells have now been recognized. Th17, characterized by the production of interleukin (IL)-17 and IL-22, promote potent inflammatory responses [4]. Tregs on the other hand limit inflammation and subsequent tissue damage [5]. A reciprocal relationship exists between Th17 and Tregs.

Coincident with the reduction in the viral load upon ART initiation, an increase in immune effector cells occurs in HIV-infected patients. The initial expansion is seen in memory $CD4^+$ lymphocytes and is attributable to redistribution rather than cell proliferation. After 4–6 weeks, naïve $CD4^+$ cells begin to increase. Advanced HIV infection is also associated with depletion of Tregs [6]. HIV induces Tregs accumulation in lymphoid tissue [7] and ART causes reversal of this migration [6].

Several lines of evidence suggest that IRS represents exaggerated pathogen-driven effector response or failure of regulatory response to restrain these [8,9]. That IRS is

an antigenic-driven inflammatory response was suggested by the fact *Mycobacterium avium*-infected T-cell-deficient mice upon inoculation with $CD4^+$ T cells rapidly succumbed to IRS [10•]. Defects in the number or function of Tregs have also been proposed to characterize IRS. The ability of Tregs to induce suppression was compromised despite their expansion during IRS [11]. On the other hand, no compromise in the number and function of Tregs was documented in cytomegalovirus immune recovery uveitis [12]. Cryptococcal and tuberculosis (TB)-associated IRS coincided with a peak in activated T cells and pathogen-specific interferon (IFN)-γ responses and did not reflect a paucity of regulatory T cells [13].

Th1/Th17 are also the key mediators of allograft rejection and targets of immunosuppressive agents employed in transplant recipients, whereas Tregs/Th2 promote graft tolerance [14]. The cumulative effect of immunosuppression in transplant recipients is induction of tolerance by suppression of Th1/Th17 and upregulation of Th2, with or without Treg expansion. The basis of posttransplant IRS is believed to be reversal of anti-inflammatory to proinflammatory responses as a result of withdrawal of iatrogenic immunosuppressive agents and employment of antimicrobial therapy that reverts pathogen-induced immunosuppression [14] (Table 1).

It is plausible that immunomodulatory characteristics of specific antifungal drugs may contribute to microbial pathogenesis and IRS [37]. Amphotericin B deoxycholate upregulates the transcription of inflammatory cytokines. The lipid formulations of the polyenes on the other hand downregulate or have no effect on inflammatory cytokine expression [38]. Echinocandins unmask β-glucan and have the potential to illicit inflammatory cytokine release from macrophages [39]. Voriconazole enhanced phagocytic proinflammatory activity by upregulation of Toll-like receptor 2 mediated by nuclear factor-κB [40]. The significance of antifungal-agent-associated immune modulation in the context of IRS, however, remains to be defined.

HIV-associated mycoses

IRS has been reported in 17–30% of patients with cryptococcal disease [41,42]. On the basis of a review of 54 cohort studies involving 13 103 patients [3], lower baseline and higher on-treatment $CD4^+$ T-cell counts were associated with IRS. Additionally, higher baseline and lower on-treatment HIV-RNA levels pose a risk of IRS [43•]. Nadir $CD4^+$ less than 100 cells, HIV-RNA decrease greater than 2.5 log, and $CD4^+$ increase greater than 50 from initiation of ART were also risks for IRS [44]. Notably, potent ART regimens (boosted protease inhibitors and/or nonnucleoside reverse transcriptase inhibitors) were independent risk factors for IRS [44]. Direct immunomodulatory attributes of protease inhibitors, for example, antiapoptotic effects, increase in macrophage proinflammatory cytokines, and lymphoproliferation were considered to account for these findings [44].

Key points

- Immune reconstitution syndrome (IRS) represents an exaggerated pathogen-driven effector response or failure of regulatory responses to restrain these.
- Cryptococcosis-related IRS has been documented in HIV-infected patients initiating antiretroviral therapy, organ transplant recipients, and recipients of immunomodulatory agents that target tumor necrosis factor α, whereas aspergillosis-associated IRS has been reported largely in neutropenic hosts and hematopoietic stem cell transplant recipients.
- Reliable means to diagnose IRS and biomarkers that differentiate worsening disease from IRS warrant assessment.
- Although limited data have shown efficacy of corticosteroids, an optimal approach to the management of IRS remains unknown.

Pregnancy

An immunosuppressive state characterized by anti-inflammatory response is critical for the maintenance of pregnancy [45]. Maternal hormones during pregnancy enhance Th2/Treg while suppressing Th1. During the postpartum period, the shift in the immunological repertoire towards Th1 may be associated with a physiologic or even pathologic inflammatory response [46] that is conducive to quiescent or latent infections manifesting as symptomatic disease. IRS during the postpartum period has been summarized in a recent review article [46].

Immune reconstitution syndrome associated with iatrogenic biologic agents

Immunomodulatory agents that target tumor necrosis factor (TNF)-α impair key antifungal host defenses, for example, formation and maturation of granulomas, recruitment of effector immune cells and pattern-recognition receptors. Consequently, these agents have been associated with various mycoses. Of 281 invasive mycoses in the recipients of TNF-α inhibitors, 80% were associated with infliximab, 16% with etanercept, and 4% with adalimumab [47]. A vast majority of these were due to histoplasmosis followed by candidiasis and aspergillosis. IRS was observed in 42% (8/19) of patients with histoplasmosis upon discontinuation of TNF inhibitors [1•] and manifested most frequently as respiratory failure; however, pulmonary nodules, lymphadenopathy, liver

Table 1 Characteristics of immune reconstitution syndrome associated with fungal infections

Fungal pathogen or disease	Hosts in which IRS documented	Pathogenic basis	Clinical manifestations	References
Invasive aspergillosis	Hematologic malignancy and HSCT recipients	Recovery from neutropenia, particularly if abrupt, enhanced chemotaxis and release of proinflammatory cytokines	Worsening imaging findings, respiratory failure, hemoptysis, pneumothorax	[15–17]
Cryptococcus neoformans	HIV-infected patients initiating ART	Restoration of effector T cells in the setting of profound immunodeficiency and/or defects in regulatory responses (T regs) to restrain these	Aseptic meningitis, cerebral mass lesions, spinal arachnoiditis, hydrocephalus, pulmonary nodules, lymphadenitis, cellulitis	[18–20]
	Organ transplant recipients	Reversal of anti-inflammatory (Th2/Tregs) to proinflammatory responses (Th1/Th17) as a result of reduction of iatrogenic immunosuppression and employment of antifungal therapy that reverts pathogen-induced immunosuppression		[21–23]
	TNF-α receptor inhibitors	Reversal of cytokine profile upon withdrawal of TNF-α blockade, neutrophil proliferation and nuclear factor-κB-mediated proinflammatory response		[24]
	CD-52 antibody (alemtuzumab)	Rapid immune recovery ($CD4^+$ T cells) following cessation of lymphoablative therapy		[25]
Invasive candidiasis	Neutropenic patients	Recovery from neutropenia	Hepatosplenic or chronic disseminated candidiasis	[26,27]
	HSCT recipients	Withdrawal of immunosuppression and recovery of $CD4^+$ and $CD8^+$ lymphocytes	Central nervous system candidiasis	[28]
Histoplasma capsulatum	Organ transplant recipients	Reverting anti-inflammatory to proinflammatory responses with reduction of immunosuppression	Disseminated histoplasmosis	[29]
	TNF-α receptor inhibitors	Reversal of TNF-α blockade resulting in neutrophil and proinflammatory cytokine responses		[1•]
Pneumocystis jirovecii	HIV-infected patients initiating ART and transplant recipients	Rapid lymphocyte proliferation and recovery of $CD4^+$ cells with initiation of ART	Worsening infiltrates, hypoxia, requirement of mechanical ventilation, organizing pneumonia	[30–33]
Penicillium marneffei	HIV-infected patients initiating ART	Restoration of immunity following initiation of ART	New onset or progression of preexisting skin lesions	[34–36]

ART, antiretroviral therapy; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplant; IRS, immune reconstitution syndrome; Th, T-helper; TNF-α, tumor necrosis factor-alpha; Tregs, T regulatory cells.

dysfunction, and hemophagocytic syndrome were also reported. All cases recovered, although 38% required corticosteroids.

Fungal infections are also a well recognized complication of potent T-cell depleting agents such as alemtuzumab. The perturbations in the T cells following alemtuzumab include not only changes in CD4/CD8 T-cell numbers but also highly restricted T-cell repertoire especially in CD4 T cells. IRS can occur in the setting of T-cell reconstitution after alemtuzumab therapy [25]. An IRS-like syndrome following alemtuzumab has also been reported in association with *Pneumocystis jirovecii* in patients with chronic lymphocytic leukemia [48].

Cryptococcosis-associated immune reconstitution syndrome

Cryptococcosis is the most frequently described infection associated with IRS in the solid organ transplant (SOT) population [14,49]. Certain characteristics of this yeast, for example, its ability to elicit mitogenic responses that are highly inflammatory, may partly account for these observations. Preferential inhibition of Th1 with induction of Th2 that compromises host resistance is another unique attribute of *Cryptococcus*. Reversal of Th2 with appropriate antifungal therapy and concurrent reduction of immunosuppression is proposed to be the basis of IRS after cryptococcosis [14].

An estimated 5–11% of the SOT recipients with cryptococcal disease may develop IRS, typically between 4 and 6 weeks after initiation of antifungal therapy. IRS occurred more frequently in patients receiving potent immunosuppressive treatment comprising tacrolimus, mycophenolate mofetil (MMF), and prednisone, and in those with disseminated disease [23]. IRS may present as lymphadenitis, cellulitis, aseptic meningitis, cerebral mass lesions, spinal arachnoiditis, hydrocephalus, or pulmonary nodules. Neuroimaging findings of IRS include parenchymal lesions with brain edema, leptomeningeal enhancement, and hydrocephalus. In renal transplant recipients with cryptococcosis, the allograft was lost to rejection in 66% of those with IRS compared with 5.9% of those without IRS ($P = 0.012$) [50].

Aspergillosis-associated immune reconstitution syndrome

Well before IRS was recognized, it was observed that patients with hematologic malignancies developed worsening pulmonary infiltrates during neutrophil recovery. The rapidity of neutrophil increase was critical for the development of the above complications; patients with rapid PMN recovery were more likely to develop these complications than those without it [17]. In 19 neutropenic patients with proven or probable invasive pulmonary aspergillosis, including 7 hematopoietic stem cell transplant (HSCT) recipients, the mean time to IRS after an absolute neutrophil count greater than 100/μl and greater than 500/μl was 3.5 and 2 days, respectively [2]. Clinical presentation consisted of worsening or new onset of hypoxia, cough, chest pain, dyspnea, and hemoptysis [2]. Radiologic findings included increasing and/or new-onset pulmonary infiltrates, pleural effusion, nodular lesions, intrathoracic lymphadenopathy, and cavitation [2]. Declining titers of sequential serum galactomannan were observed in all. Three patients died and autopsies failed to identify invasive aspergillosis as the cause of death. The other 16 patients improved; however, two required methylprednisone for impending respiratory failure [2].

Hepatosplenic candidiasis

This entity, also known as chronic disseminated candidiasis, is observed in approximately 5% of the neutropenic patients with acute leukemia. Several lines of evidence suggest that hepatosplenic candidiasis is a manifestation of IRS [26,27]. It develops during the period of neutrophil recovery, blood and other fungal cultures are typically negative, liver biopsy shows focal inflammatory granulomatous lesions with T-lymphocyte infiltration, and the response to antifungal therapy is protracted or erratic [26]. Rapid resolution of symptoms has been observed upon employment of corticosteroids with antifungal therapy [26,27].

Immune reconstitution syndrome associated with other fungi

P. jirovecii-associated IRS developed within 2 weeks of completing treatment and was temporally related to initiation of ART and either withdrawal or decrease of prednisone [32]. Each of the patients had experienced a 3-log decline in plasma HIV-RNA and had worsening infiltrates and hypoxia that required supportive mechanical ventilation. Lung biopsy revealed organizing pneumonia associated with *P. jirovecii* [31].

Other mycoses-related IRS includes candidiasis [28], spondylodiscitis caused by *Dipodascus capitatus* [51], *Penicillium marneffei* [36], *Sporothrix schenckii* [52], *Coccidioides* lymphadenopathy [53], and disseminated histoplasmosis [29,54].

Diagnostic markers

Predictive and diagnostic biomarkers of IRS that distinguish it from progressive disease have yet to be determined. In patients with cryptococcal meningitis who

initiated ART, lower cerebrospinal fluid (CSF) WBC, protein, IL-6, IL-8, and IFN-γ at baseline were predictive of subsequent IRS, whereas each two-fold increase in IL-8 was protective (odds ratio 0.32) [55•]. The combination of initial CSF WBC count of 25 cells/μl or less and CSF protein levels of 50 mg/dl or less was associated with the development of IRS with a sensitivity of 69% and specificity of 76% [55•]. In a cohort of HIV-positive ART-naïve patients who began ART, pre-ART D-dimer and C-reactive protein were significantly elevated in IRS compared with non-IRS controls [56]. Furthermore, compared with non-IRS controls, IRS cases had significantly higher plasma D-dimer concentrations at month 1, which approximated the onset of IRS [56]. Hypercalcemia can be a helpful clue for the presence of IRS. Initiation of granuloma formation relies on Th1 cytokines, and 1α-hydroxylase of activated macrophages substantially increases the synthesis of $1,25(OH)_2$ vitamin D3 resulting in hypercalcemia [57–59]. Finally, polymorphisms in cytokine genes may play a role in host susceptibility to IRS [56,60].

Treatment

Therapeutic modalities attempted for IRS include corticosteroids, intravenous immunoglobulin, nonsteroid anti-inflammatory agents, and biologic immunomodulators. Case reports and small series have documented the efficacy of corticosteroids for IRS [61,62]. In a randomized trial of TB-related IRS in HIV-infected patients, prednisone reduced the duration of hospitalization, and led to more rapid clinical improvement and markers of inflammation [63•]. Corticosteroids, however, are not optimal agents for the treatment of IRS. Given the potential for adverse sequelae and nonspecific immunosuppressive effect, their use for IRS remains a concern. Furthermore, there is mechanistic basis by which corticosteroids may in fact worsen inflammation rather than suppress it [64].

TNF-α plays a role in recruiting inflammatory cells and in granuloma formation, and its inhibitor infliximab has been successfully employed for IRS refractory to high-dose corticosteroids and cyclophosphamide in a patient with CNS TB [65]. Given their anti-inflammatory attributes, a role for statins has been proposed in IRS [66•]. These agents promote the development of Th2/Tregs and inhibit Th1/Th17 [67]. Statins also intervene with the function of antigen-presenting cells [67]. A beneficial effect of these drugs has been shown for other inflammatory disorders, for example, experimental autoimmune arthritis and myocarditis [68]. In patients undergoing T-cell replete allogeneic HSCT, a lower rate of grade II–IV graft versus host disease was observed in statin recipients than in those not receiving these agents [69]. Paradoxically, the capacity to mount protective immune responses to pathogens and cognate antigens is not diminished with statins [70]. Future studies are warranted to investigate the effects of statins alone or in combination with other agents for the management of IRS.

Prevention

An important consideration is the management of immunosuppression so as to curtail the risk of IRS. As rapid reduction or withdrawal of immunosuppressive agents might predispose SOT recipients to IRS, it is prudent to space or separate initiation of antimicrobial agents and reduction in immunosuppression to minimize the risk of IRS and allograft loss. The goal should be gradual tapering as opposed to abrupt cessation with consideration given to reduction of corticosteroids first.

Whether deferring the initiation of ART for approximately 4 weeks, that is, until the infection is microbiologically controlled, reduces IRS risk has been a matter of significant controversy. Initiation of ART closer to the diagnosis of an opportunistic infection has been associated with the development of IRS in at least two retrospective studies [19,20]. A randomized trial of early ($\leq$72 h) versus delayed ART (10 weeks of therapy) in patients with cryptococcal meningitis documented three times higher mortality in the early ART group with overall duration of survival of 28 versus 637 days in the two groups, respectively ($P = 0.031$) [71]. Most deaths occurred in the first 4 weeks and were considered attributable to cryptococcal meningitis. Although precise reasons for poorer outcome after early ART initiation were not known, a systematic assessment of IRS was not performed [71]. Early ART, however, did not increase the risk of IRS in a randomized trial on non-TB HIV-associated opportunistic infection [43•]; 6.3% of the patients treated early experienced IRS versus 10.4% who received deferred ART. Likewise, in two prospective studies of cryptococcal IRS, earlier ART was not associated with the development of IRS [41,42]. The receipt of corticosteroids during the management of the acute opportunistic infection was not significantly associated with a reduction in the overall risk of immune reconstitution inflammatory syndrome [43•].

Conclusion

IRS remains a poorly understood entity and studies to assess its diagnostic biomarkers and distinguish it from worsening disease warrant assessment. These biomarkers should ideally be amenable to testing in real time. Future studies should also assess optimal reduction of immunosuppression in patients with opportunistic mycoses and therapeutic approaches for the management of IRS.

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Conflicts of interest

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 613).

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